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Brief Report

Headache in 25 consecutive patients with atrial septal defects before and after percutaneous closure – A prospective case series

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Key words: migraine with aura, migraine without aura, atrial septal defect, cardiac shunts

Abstract

In contrast to patent foramen ovale, that is highly prevalent in the general population, atrial septal defect (ASD) is a rare congenital heart defect. The effect of ASD closure on headache and migraine remains a matter of controversy. The objectives of the study were (i) to determine headache prevalence in consecutive patients with ASD scheduled for percutaneous closure for cardiologic indications, using the classification of the International Headache Society and (ii) to compare headache characteristics before and after closure of ASD. In this observational case series no a priori power analysis was performed. Twenty-five consecutive patients were prospectively included over 27 months. Median duration of follow-up was 12 months, [Interquartile range 0]. Prevalence of active headache seemed to be increased compared to the general population: Any headaches 88% (95% confidence interval 70-96), migraine without aura 28% (14-48), migraine with aura 16% (6-35). After ASD closure, we observed a slightly lower headache frequency (median frequency 1.0 [2.6] vs. 0.3 [1.5] headaches per month; p=0.067). In patients with ongoing headaches, a significant decrease in headache intensity (median VAS 7 [3] vs. 5 [4]; p=0.036) was reported. Three patients with migraine with aura before the intervention reported no migraine with aura attacks at follow-up, two of them reported ongoing tension-type headache, one migraine without aura. In summary, this prospective observational study confirms the high prevalence of headache, particularly migraine, in ASD patients and suggests a possible small beneficial effect of ASD closure.

Abbreviations: ASD…atrial septal defect, MwA…migraine with aura, MwoA…migraine without Aura, p…probable, ETTH…episodic tension-type headache, CTTH…chronic tension-type headache.

Introduction

In recent years an increased prevalence of cardiac shunts in patients with migraine with aura (MwA) has been reported (1-2). There is evidence, mostly from retrospective case series, that migraine can substantially improve or disappear after closure of a patent foramen ovale (PFO) or an atrial septal defect (ASD)(3-4). In those studies, migraine was a comorbid condition and not the cause for shunt closure. Of note, the only prospective, randomised, sham-controlled trial to assess the effect of PFO closure on MwA was negative (5). The present study was motivated by the observation that ASD closure can exacerbate migraine auras (6-7) . To date the influence of ASD closure on migraine is not clear. Case series reporting exacerbation or new appearance of MwA after this intervention contrast with studies reporting improvement (3, 8) . The objectives of the study were (i) to determine headache prevalence in consecutive patients with ASD using the classification of the International Headache Society (9) and (ii) to compare headache characteristics before and after closure of ASD in a prospective study.

Methods

The study was approved by the ethics committee of the Medical University of Vienna. From January 2006 until March 2008, unselected patients with secundum ASD, who were scheduled for interventional closure for cardiologic indications at the Department of Cardiology, Medical University of Vienna, were investigated by a neurologist (FR) on the day before the intervention after informed consent. Headache diagnoses were made based on the classification of the International Headache Society (ICH-D II) (9). Frequency, duration and intensity of headaches were recorded, as well as frequency of auras. Intensity was measured using the visual analogue scale (VAS) from 0-10 cm. All patients underwent catheter closure with an Amplatzer septal occluder device guided by transesophageal echocardiography. Transthoracal echocardiography was performed one day, 8 days, and 3 months after the procedure. 100 mg ASS / day for 6 months was started as a routine prophylaxis one day before the intervention. Some patients remained on phenprocoumon, or clopidogrel, depending on comorbidities (Table 1). All patients were followed-up by the same neurologist one week and 12 [Interquartile range 0] months after the intervention by telephone-interview.

Statistics:

As this was an observational study, no a priori power analysis was performed. Headaches prevalences given in per cent with 95% CI (Wilson) were compared to literature data from Austria (10), where available (all headaches, MwoA, MwA), or global prevalence data (tension-type headache)(11). Because there were more women than men (16:9) in our patient sample, increased headache prevalence compared to the general population with

approximately equal numbers of women and men might be observed. Therefore, prevalence data from the literature adjusted for gender distribution in our sample were also provided:

Adjusted prevalence = [16 x (prevalence in females) + 9 x (prevalence in males)] / 25.

Frequency, duration, and intensity of all headaches and migraine, as well as frequency of auras were compared before and 12 months after the intervention. Assuming that data are not normally distributed, values are presented as median and interquartile range [IQR]. The non parametric paired Wilcoxon signed-rank test was used to compare variables before and after the intervention. All $p<0.05$, two-tailed, were considered significant. Headache frequency was considered the main outcome parameter. For headache duration and intensity, only patients with ongoing headaches at follow-up were considered. In case of significant differences, the median decrease or increase was calculated to provide a measure of effect size. SPSS for Windows, Version 12.0, was used for calculations. Correction for multiple comparisons was not performed.

Results

Headache prevalence

An outline of case histories with demographic and clinical data is presented in Table 1. Twenty-five patients (16 women; median age 50 [25] years) were included into the study. In two patients, ASD was not closed (one patient refused intervention and in one the defect was found to be too large for closure at balloon stretched diameter measurement), one patient was lost during follow-up after 3 months (P11, no change in infrequent episodic tension-type headache (TTH) until then). These three patients were excluded from longitudinal analyses. None of the patients reported complications, in none of them residual shunt was found in echocardiographic controls.

Prevalence for any headaches (88%; 95% CI 70-96), MwoA (28%; 14-48), and MwA (16%; 6-35) seemed to be higher compared to literature data from the general population (Table 2). Prevalence for tension-type headache (40%; 23-59) was comparable to the general population.

Headache frequency, duration, and intensity

Results for these parameters are summarized in Table 3. Considering all patients, median headache frequency decreased from 1.0 [2.6] headaches per month before the intervention to 0.3 [1.5] headaches per month after the intervention ($p=0.067$; Fig. 1). Considering only

migraine, median monthly attack frequency was 1.5 [3.9] before and 0.33 [0.9] after the intervention (n.s.; Fig. 2). Headache duration was not significantly changed before and after the intervention. Considering all patients with ongoing headaches, pain intensity was significantly lower after the intervention (median VAS 7 [3] before vs. 5 [4] after; p=0.036). The median reduction in VAS was 0.25 [2.75]. Considering only patients with ongoing migraine attacks, headache intensity was unchanged (Table 3).

Observations in single patients with migraine

In 3 migraine with aura (MwA) patients, no auras were reported 6 months after the intervention (follow up 20 months), in one MwA patient, attack frequency decreased markedly, in one patient with probable MwA, attack frequency remained unchanged (Fig 3). In the 3 patients in who reported no auras at follow-up, episodic tension-type headache (ETTH) (P15, P22) or MwoA (P24) persisted at low frequencies. One patient with MwoA and ETTH (P8) reported no migraine attack after the intervention, but ETTH persisted (Table 1).

An increased attack frequency of MwoA was observed in 3 patients 3 months after ASD closure (P13, P16, P17). Attack frequency decreased to baseline or below at 6 months in these patients. A single prolonged aura during a migraine attack was observed in one patient (P24) about three months after ASD closure.

Discussion

In contrast to PFO that is highly prevalent in the general population, ASD is a rare condition that affects only 1-3 per 10 000 births (12). The prevalence of headache, particularly migraine, in consecutive patients with ASD seemed to be increased compared to the general population, which is in accordance with previous studies reporting prevalences of 11-22% for MwA and 12-19% for migraine without aura (MwoA) (3, 8, 13) in this patient group. Large confidence intervals in our sample represent uncertainty in the given sample size. To the best of our knowledge it is currently not clear, whether the prevalence of ASD is elevated among patients with migraine. The prevalence of right-to-left shunts –most frequently related to a PFO- was found elevated in MwA (1-2), although this has been challenged recently (14). Nevertheless it is believed that microemboli can evoke cortical spreading depression which probably underlies migraine aura in a subgroup of patients (14). This could explain an association between MwA and cardiac shunts. Alternatively, inheritance of common genetic

factors for cardiac defects and migraine with aura has been suggested. Common inheritance of atrial shunts including ASD with migraine with aura was observed in some families (15).

Considering all types of headache, a slightly lower attack frequency after ASD closure was observed, although this was not significant, possibly because of the small sample size. Taking into account all headache types in patients with ongoing headaches, intensity was significantly lower after ASD closure. A statistically significant change in the VAS does not imply a meaningful reduction in pain for most of patients. The median reduction in VAS was only 0.25.

Three patients with MwA before the intervention reported no auras at follow-up. However, other headaches (ETTH or MwoA) persisted at low frequencies. In addition, two of these patients had only rare auras before the intervention, suggesting a declining natural course. These patients were on oral anticoagulation or antiplatelet therapy already before ASD closure so that an effect of medication can be considered unlikely.

An increased attack frequency of MwoA was observed in 3 patients 3 months after ASD closure. Attack frequency decreased to baseline or below at 6 month in these patients. A single prolonged aura during a migraine attack was reported by one patient about three months after ASD closure, probably without any relation to the intervention.

In none of the patients we observed an increase in headache attacks in the first week after the intervention; in none of them we observed de novo migraine. One patient, who was diagnosed probable chronic tension-type headache, suffering from daily headaches before the intervention, remained completely headache free thereafter. We suggest that this patient might have suffered from headache attributed to hypoxia, since an association between tension-type headache and cardiac shunts seems unlikely.

Only a few studies systematically investigated the effect of ASD closure on migraine. In one prospective (8) and one retrospective (3) study, respectively, a significant decrease in migraine prevalence was found after ASD closure, particularly in MwA. However several shortcomings of these studies merit discussion. In the study of Luermans et al (8), migraine was assessed prospectively using questionnaires based on IHS diagnostic criteria in 68 patients with ASD, albeit only 84% of patients returned questionnaires 12 months after the intervention. About half of those who did not return questionnaires were considered suffering from migraine before the intervention; therefore the question of response bias arises. The study of Azarbal and co-workers (3) was a retrospective evaluation of headache based on self-report of patients on the basis of a diagnosis made by either their primary care physician or

their neurologist. It included 26 patients with ASD. Diagnostic headache criteria were not used.

In another retrospective study using questionnaires no influence on migraine prevalence was noted at least 6 months after the intervention in 114 patients with ASD (13). In this study several patients developed de novo migraine that disappeared at long-term follow-up (16). An increased attack frequency or de novo development of migraine, mostly with aura, has been repeatedly reported (6, 17-19) in single cases or case series. Sharifi et al (19) reported response of these "post ASD closure headaches" to a loading dose of 300 mg clopidogrel followed by 75 mg/d clopidogrel for 6 months. In a retrospective analysis, Rodes-Cabau et al found de novo migraine in 12% of patients after closure of an ASD, who were migraine free before the intervention (17). In two thirds of these patients, migraine persisted 2 years after the intervention.

Limitations of the present study are the sample size and the open design. A small beneficial effect of ASD closure is suggested. A placebo-effect can be considered unlikely, since ASDs were closed for cardiologic reasons and patients had no expectations concerning improvement of their headaches. After ASD closure most patients received platelet inhibitors until 6 months after the intervention, whereas clinical data were recorded 12 months thereafter. Three patients, who remained on platelet inhibitors or oral anticoagulation at follow-up, were on either platelet inhibitors or oral anticoagulants already before the intervention. Therefore, modifications of anticoagulant/antiplatelet therapy are unlikely to be a confounder.

Strength of this series is that all patients were seen and prospectively followed up by a neurologist, making headache diagnoses based on the most recent IHS classification. All types of headaches were considered.

In summary, this observational study confirms the high prevalence of headache, particularly migraine, in ASD patients. In addition, it suggests a small beneficial effect on headache in the long run, although a transient increase in attack frequency was observed in a few patients. We conclude that the relationship between ASD and migraine deserves further systematic investigation, for instance with case-control studies.

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Table 1: Clinical features in 25 consecutive patients scheduled for ASD-closure for cardiologic indications. Abbreviations: MOH … medication overuse headache MwoA…migraine without aura, MwA… migraine with aura. p…probable, ETTH…episodic tension-type headache, CTTH…chronic tension-type headache.

Patient	Age/sex	ICH D-II diagnoses	Clinical comments
P1	49/m	MwoA, MOH	ASD was not closed on the patient's choice. He suffered from ischemic stroke after 10 months.
P2	25/m	-	No headaches reported
P3	58/f	MwoA	Minor stroke several months before the intervention with right-sided hemihypesthesia and residual aphasia. Clopidogrel 75 mg/month. An MRI before ASD closure showed a small infarct in the left internal capsule and thalamus, an MRI on the day after ASD closure was unchanged. She noted a decrease in headache frequency. Clopidogrel was continued.
P4	52/f	MwoA	This patient had been on phenprocumon several months before the intervention. She remained on it one year after the ASD closure. No change in headache frequency reported.
P5	49/m	pMwoA	Before closure he fulfilled diagnostic criteria for MwoA, except duration of 3.5 h. Headaches unchanged 14 months after ASD closure.
P6	75/f	Infrequent ETTH	Suffers from headache only rarely, no change experienced
P7	68/f	Infrequent ETTH	Phenprocuomon before intervention, phenprocumon + ASS after intervention for 6 months. No change reported
P8	51/f	MwoA, ETTH	This patient took ASS one month before intervention. She suffered from a typical migraine with aura attack one day after the intervention; since then no migraine headaches had occurred, but she suffered from episodic tension type headaches about twice/month (takes medication).
P9	70/f	Infrequent ETTH	Only rare headaches before and after the intervention (once every 4 months). No headaches after 6 months. (Follow-up 12 months)
P10	25/f	pMwoA	Before intervention 1-2 headaches/months. Decrease after intervention. No headaches 12 months after the intervention.
P11	29/m	Infrequent ETTH	No change after 3 months. Lost during follow-up.
P12	39/f	ETTH	Initial headache frequency 1/month; remained unchanged after 3 and 6 months. At 12 months 3 headaches/month
P13	42/f	MwoA	Increase in attack frequency after 3 months to 4 headaches/months. After 6 months headache frequency similar to before the intervention with 1-2/month
P14	59/f	Infrequent ETTH	ASD was not closed because the balloon stretched diameter was too large. The patient refused surgery.
P15	66/f	ETTH, MwA (typical aura without migraine headache)	Since young adulthood typical MWA (several attacks/month). Nine years ago she suffered from minor stroke with left-sided hemiparesis, the diagnosis of ASD was made and she was set on phenprocomon. She experienced a significant reduction of her auras, headaches disappeared, which the patient attributed to her retiring. The patient had Typical aura 5 months after the intervention; another one week later, no headache at both instances. Since then no auras.
P16	41/f	MWA , MWOA after intervention	This patient was on ASS 100 mg/d and 1.25 mg/d bisoprolol before the intervention. Clopidogrel was added after ASD closure, Nabivolol for hypertension. Three months after intervention frequent migraine without aura with use of caffeine + ergotamine, diagnostic criteria for MOH were not fulfilled. Six months after the intervention, attack frequency decreased below baseline (less than one headache/month).
P17	38/m	pMwoA	Minor stroke with aphasia and left-sided hemiparesis 8 months ago led to diagnosis of ASD. Oral anticoagulation with phenprocoumon was started. Three weeks after ASD closure almost daily holocranial pulsating headache worsened by movements without vegetative symptoms, which lasted until three months after the intervention. Six months after the intervention only rare headaches (once every three months). One year after the intervention the patient was still on

			ASS 100 mg/d
P18	40/f	pMWA, pMwoA	Recurrent headaches lasting for 2 weeks. Visual aura most of times. No change observed.
P19	81/m	-	No headaches reported
P20	42/f	MwoA	MwoA for five years. Relief of headaches after frovatriptan 2.5 mg. No change after ASD closure reported
P21	77/f	-	No headaches reported
P22	58/f	MWA, ETTH	MWA since age of 35 and ETTH once / month. Typical visual aura (fortification spectra) 1-2/month with attack free periods up to three months. Headaches became less intense over time, but auras continued in the same frequency. ASD was diagnosed because of dyspnoea when walking upstairs. After ASD closure she received lisinopril 5 mg/d for hypertension. She suffered from visual auras associated with photophobia and nausea twice five 5 months after the intervention with an interval of one week. In general, she feels much better after the intervention and can easily walk upstairs. No more auras since then (Follow-up 20 months). ETTH unchanged
P23	35/f	pCTTH	Daily “pressure” behind left eye without accompanying symptoms, onset unclear. ASD was diagnosed because of dyspnoea. Complete relief of headache one week after the intervention (Follow-up 20 months). Feels much better in general.
P24	59/f	MwoA MwA	MwA and MwoA for several years, MwA frequency several times/year. Migraine attacks were sometimes associated with vertigo. ASD discovered during routine work-up. Before the intervention the patient was on ASS, clopidogrel, bisoprolol. Three months after ASD closure prolonged visual aura during migraine attack. Since then no auras (Follow-up 20 months). MwoA less frequent, less intense
P25	43/f	ETTH	ETTH for 5 years. No change experienced

Table 2
Headache prevalence in 25 consecutive patients with ASD compared to literature data for the general population. *Adjusted for gender distribution, see text.

Headache diagnosis	Present study % (N)	95% CI	General population	
			%	% adj.
Migraine with aura	16.0 (4)	(6-35)	2.3	2.5*
Migraine without aura	28.0 (7)	(14-48)	5.6	6.1*
Tension-type headache	40.0 (10)	(23-59)	38.0	41.5*
No headache diagnosis	12.0 (3)	(4-30)	51.6	49.3*
Probable migraine with aura	4.0 (1)	(1-25)		
Probable migraine without aura	16.0 (4)	(6-35)		
Probable chronic tension-type	4.0 (1)	(1-25)		

Table 3
Headache characteristics in 22 ASD patients before and after percutaneous ASD closure. For duration and frequency, only patients with ongoing headache attacks were considered. Values are presented as median (interquartile range in brackets).

All Headaches	**Before**	**After**	**Wicoxon signed- rank test**
Frequency Headaches/month	1.0 [2.6]	0.3 [1.5]	p=0.067
Duration h	4.3 [9.5]	3.5 [9.6]	n.s.
Intensity VAS	7 [3]	5 [4]	p=0.036
Migraine	**Before**	**After**	
Frequency Headaches/month	1.5 [3.9]	0.33 [0.9]	n.s.
Duration h	4.3 [15.6]	6.0 [47.5]	n.s.
Intensity VAS	7.25 [1.9]	6.5 [2.6]	n.s.

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Figure 1: Headache frequency in consecutive patients with ASD before and after percutaneous ASD closure

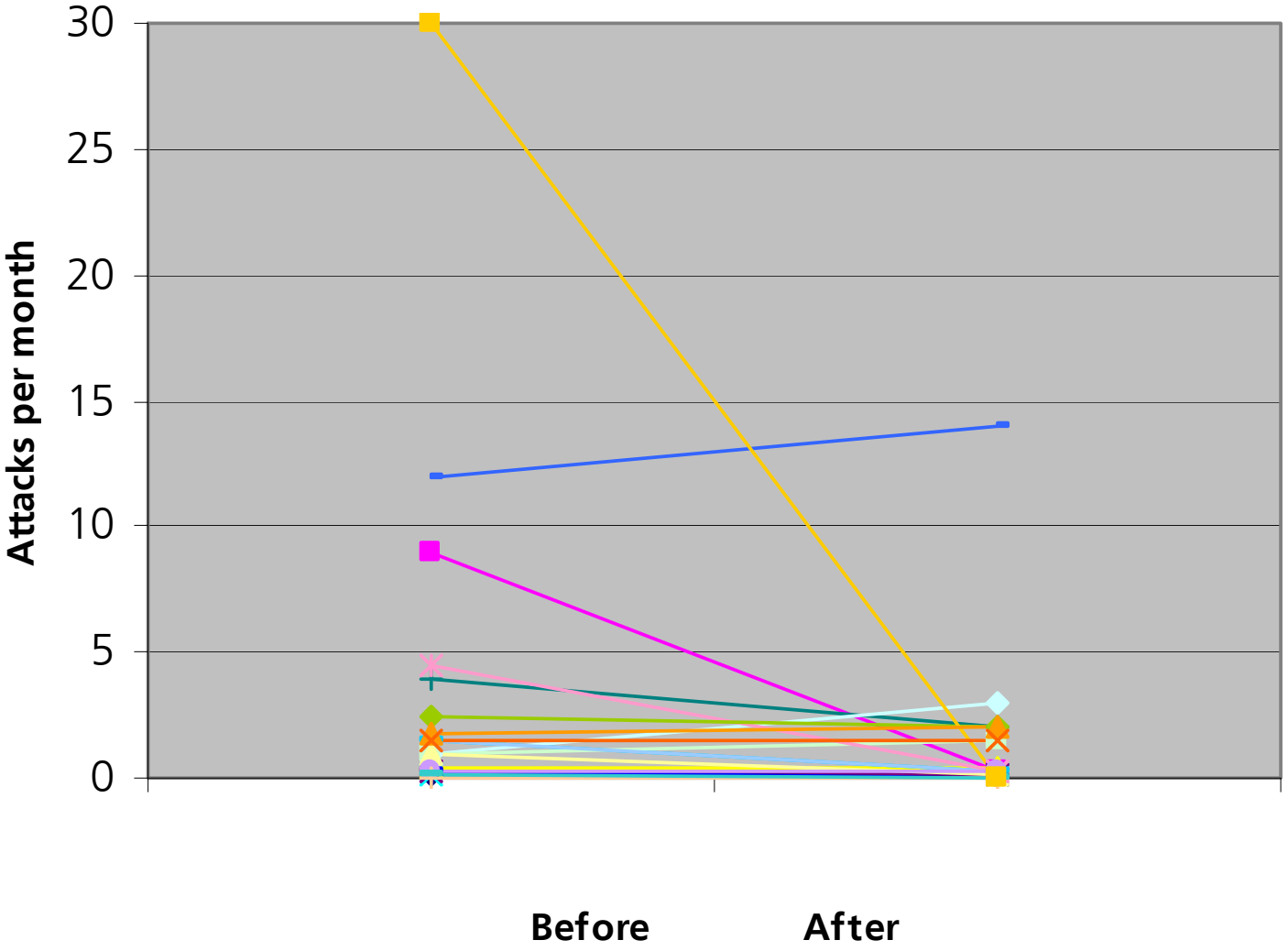

Figure 2: Attack frequency in consecutive atrial septal defect (ASD) patients with migraine with and without aura before and after percutaneous ASD closure

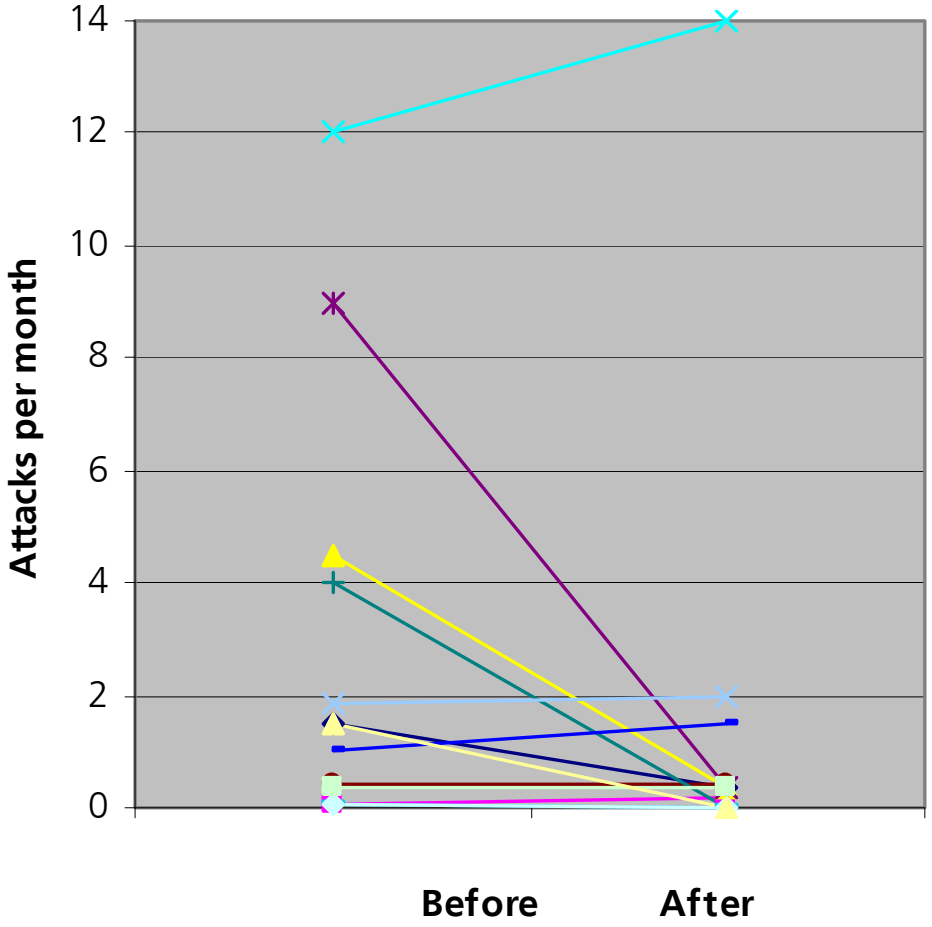

Figure 3: Attack frequency in consecutive atrial septal defect (ASD) patients with migraine with aura and probable migraine with aura before and after percutaneous ASD closure